Clinical trial results:
Phase III, randomised, double-blind, stratified comparative, placebo controlled, parallel group, multicentre study to assess the effect of deep subcutaneous injections of lanreotide Autogel 120 mg administered every 28 days on tumour progression free survival in patients with non functioning entero-pancreatic endocrine tumour.

Summary

EudraCT number	2005-004904-35
Trial protocol	GB NL BE DK CZ GR SE DE AT IT SK ES
Global end of trial date	09 April 2013
Results information	
Result version number	v1 (current)
This version publication date	04 June 2016
First version publication date	04 June 2016

Trial information

Trial identification	
Sponsor protocol code	Protocol2-55-52030-726
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	IPSEN PHARMA SAS
Sponsor organisation address	65 quai Georges Gorse, Boulogne Billancourt Cedex , France, 92650
Public contact	Medical Director, Gastroenterology, Ipsen Pharma S.A.S, clinical.trials@ipsen.com
Scientific contact	Medical Director, Gastroenterology, Ipsen Pharma S.A.S, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2013
Global end of trial reached?	Yes
Global end of trial date	09 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the effect of lanreotide Autogel 120 mg administered every 28 days compared to placebo, on progression-free survival in patients with well or moderately differentiated non functioning entero-pancreatic endocrine tumour.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	India: 4
Worldwide total number of subjects	204
EEA total number of subjects	170

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	111
From 65 to 84 years	91
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

264 subjects were screened at 48 investigational sites in 14 countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, India, Italy, Poland, Slovakia, Spain, Sweden, United Kingdom and the United States of America). 204 subjects were randomised to receive study treatment in the Intent to treat (ITT) population.

Pre-assignment

Screening details:

A total of 264 subjects were screened for this study. There were 101 subjects randomised to receive lanreotide Autogel 120 mg and 103 subjects randomised to receive placebo. These 204 randomised subjects form the ITT population for analysis.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Two sets of individual sealed code break envelopes were prepared by an Ipsen Randomisation Manager to enable code break procedures of individual subjects without compromising the blind of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanreotide (Autogel Formulation)

Arm description:

120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

Arm type	Experimental
Investigational medicinal product name	Lanreotide Autogel 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg

Arm title	Placebo

Arm description:

Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NA

Number of subjects in period 1	Lanreotide (Autogel Formulation)	Placebo
Started	101	103
Completed	56	34
Not completed	45	69
Consent withdrawn by subject	3	5
Physician decision	6	9
Disease progression	27	49
Not otherwise specified	4	1
Adverse event	3	3
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Lanreotide (Autogel Formulation)
Reporting group description:	
120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.	

Reporting group values	Lanreotide (Autogel Formulation)	Placebo	Total
Number of subjects	101	103	204
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63	62	
standard deviation	± 10	± 11	-
Gender categorical Units: Subjects			
Female	48	49	97
Male	53	54	107
Race (NIH/OMB) Units: Subjects			
Asian	2	5	7
Black or African American	2	2	4
White	97	96	193
Neuroendocrine tumour (NET) origin Units: Subjects			
Pancreas	42	49	91
Midgut	33	40	73
Hindgut	11	3	14
Unknown/Other	15	11	26
Chromogranin A			
Chromogranin A is an NET marker. ULN: upper limit of normal			
Units: Subjects			
≤1 × ULN	33	34	67
1–2 × ULN	25	18	43
>2 × ULN	41	48	89
Unknown	2	3	5
Time since diagnosis Units: months			
arithmetic mean	32.6	34.4	
standard deviation	± 46.1	± 41.4	-
5-HIAA			
n= 44 and 37			

Units: µmol/d			
arithmetic mean	163.2	285.8	
standard deviation	± 194	± 406.4	-
Gastrin			
n = 33 and 35			
Units: ng/L			
arithmetic mean	258.4	450.3	
standard deviation	± 220	± 353.2	-
Pancreatic polypeptide			
n = 29 and 34			
Units: pmol/L			
arithmetic mean	164.03	167.43	
standard deviation	± 35.53	± 38.81	-

End points

End points reporting groups

Reporting group title	Lanreotide (Autogel Formulation)

Reporting group description:

120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

Reporting group title	Placebo

Reporting group description:

Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[1][2]

End point description:

Time from randomization to first documentation of disease progression, or death. Disease progression centrally assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0

Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects.

For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached during the 96 week fixed duration study.

End point type	Primary

End point timeframe:

From randomisation up to the last tumour assessment (scheduled at 96 weeks). Radiological scans were performed every 12 weeks during the first year and every 24 weeks during the second year

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to system limitations, data is presented for single arm. Hence statistical analysis details could not be included.

Statistical analyses details: P-value: < 0.001, Method: Logrank, Hazard ratio (HR): 0.47, 95% Confidence interval level: (0.3, 0.73)

The log rank test was stratified according to progression status at baseline and prior therapy. No p-value adjustment for multiple comparisons.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached during the 96 week fixed duration study. Due to system limitations, data cannot be represented for this arm, hence this arm is not included.

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Weeks				
median (confidence interval 95%)	72 (48.6 to 96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Alive & Without Disease Progression

End point title	Percentage of Patients Alive & Without Disease Progression

End point description:

Percentage of patients still ongoing (or completing at Week 96) without centrally assessed disease progression or death at Weeks 48 and 96.

Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects.

End point type	Secondary

End point timeframe:

Week 48 & 96

End point values	Lanreotide (Autogel Formulation)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	103		
Units: Percentage of participants				
Week 48	66	49		
Week 96	53	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Profile of Lanreotide

End point title	Pharmacokinetic Profile of Lanreotide[3]

End point description:

Pharmacokinetic Profile of Lanreotide assessed by mean serum concentration at specified timepoints

Analysis based on the intent-to-treat (ITT) population which comprised 101 randomised subjects who received lanreotide

End point type	Secondary

End point timeframe:

Week 4, 12, 24, 36, 48, 72, 96

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only to analyze the pharmacokinetic profile of the study drug and hence placebo arm is not included

End point values	Lanreotide (Autogel Formulation)			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: ng/mL				
arithmetic mean (standard deviation)				
At Week 4 predose (n=81)	2.5 (± 0.46)			
At Week 12 predose (n=87)	5 (± 0.42)			
At Week 24 predose (n=74)	6.1 (± 0.44)			

At Week 36 predose (n=67)	6.2 (± 0.39)			
At Week 48 predose (n=62)	6.6 (± 0.45)			
At Week 72 predose (n=52)	6.8 (± 0.44)			
At Week 96 predose (n=48)	6.6 (± 0.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Global Health Status Quality of Life Assessment

End point title	Change in the Global Health Status Quality of Life Assessment

End point description:

Analysis based on the intent-to-treat (ITT) population which comprised 193 randomised subjects with valid assessment.

Transformed scores from European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire responses (QLQ)-C30. Questionnaire response scores range from 0 to 100. Higher scores indicate best possible Quality of Life.

End point type	Secondary

End point timeframe:

Week 12 to Week 96 (last visit)

End point values	Lanreotide (Autogel Formulation)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: score on a scale				
least squares mean (standard error)	-5.2 (± 3.7)	-4.9 (± 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With a Greater Than or Equal to 50% Decrease in Plasma Chromogranin A (CgA) Levels

End point title	Percentage of Patients With a Greater Than or Equal to 50% Decrease in Plasma Chromogranin A (CgA) Levels

End point description:

Analysis based on the subgroup of subjects with an elevated plasma CgA values. Subjects with a gastrinoma were excluded from the analysis.

End point type	Secondary

End point timeframe:

Week 12 to Week 96 (last visit)

End point values	Lanreotide (Autogel Formulation)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64		
Units: percentage of participants				
number (not applicable)	42.2	4.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Still Alive Based on Available Overall Survival Data

End point title	Percentage of Patients Still Alive Based on Available Overall Survival Data

End point description:

Overall survival defined as the time from randomisation to death due to any cause. Subjects were followed for overall survival beyond study completion/withdrawal via annual telephone contact until the last subject completed the study.

Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects.

End point type	Secondary

End point timeframe:

Randomisation to death or last visit, up to 321 weeks

End point values	Lanreotide (Autogel Formulation)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	103		
Units: percentage of participants	84	77		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

End point title	Time to Disease Progression[4]

End point description:

The KM (Kaplan-Meier) estimates for the time to centrally assessed disease progression are presented.

Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects.

For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached fixed duration study.

End point type	Secondary

End point timeframe:

up to 103 Weeks

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached during the 96 week fixed duration study. Due to system limitations, data cannot be represented for this arm, hence this arm is not included.

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Weeks				
median (confidence interval 95%)	72.1 (48.6 to 96.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from baseline in Tumour Marker Levels for 5-Hydroxyindoleacetic acid (5-HIAA)

End point title	Mean Change from baseline in Tumour Marker Levels for 5-Hydroxyindoleacetic acid (5-HIAA)

End point description:

ITT Subjects with Elevated Values at Baseline

End point type	Secondary

End point timeframe:

Baseline (visit 2) and 96 weeks (last post-baseline value)

End point values	Lanreotide (Autogel Formulation)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	36		
Units: µmol/d				
arithmetic mean (standard deviation)	-74 (± 136.2)	148.1 (± 237.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from baseline in Tumour Marker Levels for Gastrin

End point title	Mean Change from baseline in Tumour Marker Levels for Gastrin

End point description:

ITT Subjects with Elevated Values at Baseline

End point type	Secondary

End point timeframe:

Baseline (visit 2) and 96 weeks (last post-baseline value)

End point values	Lanreotide (Autogel Formulation)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	35		
Units: ng/L				
arithmetic mean (standard deviation)	-91.1 (± 152.2)	-21.1 (± 287.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from baseline in Tumour Marker Levels for Pancreatic polypeptide

End point title	Mean Change from baseline in Tumour Marker Levels for Pancreatic polypeptide

End point description:

ITT Subjects with Elevated Values at Baseline

End point type	Secondary

End point timeframe:

Baseline (visit 2) and 96 weeks (last post-baseline value)

End point values	Lanreotide (Autogel Formulation)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	32		
Units: pmol/L				
arithmetic mean (standard deviation)	-107.59 (± 49.49)	-10.2 (± 59.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 96 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Lanreotide (Autogel Formulation)
Reporting group description:	
120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.	

Serious adverse events	Lanreotide (Autogel Formulation)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 101 (24.75%)	32 / 103 (31.07%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			

subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypertensive crisis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 101 (0.00%)	3 / 103 (2.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 101 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 101 (2.97%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 101 (3.96%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 101 (1.98%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ileus			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 101 (0.99%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diarrhoea			
subjects affected / exposed	0 / 101 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			

subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Biliary fistula			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic necrosis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			

subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Toxic nodular goitre			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 101 (2.97%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 101 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 101 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lanreotide (Autogel Formulation)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 101 (87.13%)	92 / 103 (89.32%)	
Investigations			
Weight decreased			
subjects affected / exposed	9 / 101 (8.91%)	9 / 103 (8.74%)	
occurrences (all)	9	10	
Pancreatic enzymes decreased			
subjects affected / exposed	6 / 101 (5.94%)	0 / 103 (0.00%)	
occurrences (all)	7	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 101 (12.87%)	5 / 103 (4.85%)	
occurrences (all)	16	5	
Flushing			
subjects affected / exposed	4 / 101 (3.96%)	6 / 103 (5.83%)	
occurrences (all)	4	6	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 101 (15.84%)	11 / 103 (10.68%)	
occurrences (all)	19	19	
Dizziness			
subjects affected / exposed	9 / 101 (8.91%)	1 / 103 (0.97%)	
occurrences (all)	12	1	
Lethargy			

subjects affected / exposed	5 / 101 (4.95%)	4 / 103 (3.88%)	
occurrences (all)	13	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 101 (10.89%)	16 / 103 (15.53%)	
occurrences (all)	15	18	
Asthenia			
subjects affected / exposed	8 / 101 (7.92%)	6 / 103 (5.83%)	
occurrences (all)	8	6	
Injection site pain			
subjects affected / exposed	8 / 101 (7.92%)	4 / 103 (3.88%)	
occurrences (all)	30	10	
Oedema peripheral			
subjects affected / exposed	5 / 101 (4.95%)	7 / 103 (6.80%)	
occurrences (all)	5	12	
Pyrexia			
subjects affected / exposed	4 / 101 (3.96%)	6 / 103 (5.83%)	
occurrences (all)	6	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	35 / 101 (34.65%)	37 / 103 (35.92%)	
occurrences (all)	57	75	
Abdominal pain			
subjects affected / exposed	23 / 101 (22.77%)	18 / 103 (17.48%)	
occurrences (all)	32	34	
Vomiting			
subjects affected / exposed	17 / 101 (16.83%)	10 / 103 (9.71%)	
occurrences (all)	21	28	
Nausea			
subjects affected / exposed	15 / 101 (14.85%)	13 / 103 (12.62%)	
occurrences (all)	28	22	
Flatulence			
subjects affected / exposed	12 / 101 (11.88%)	9 / 103 (8.74%)	
occurrences (all)	13	12	
Constipation			

subjects affected / exposed	11 / 101 (10.89%)	14 / 103 (13.59%)	
occurrences (all)	13	16	
Abdominal pain upper			
subjects affected / exposed	7 / 101 (6.93%)	9 / 103 (8.74%)	
occurrences (all)	7	15	
Abdominal discomfort			
subjects affected / exposed	5 / 101 (4.95%)	3 / 103 (2.91%)	
occurrences (all)	8	4	
Dyspepsia			
subjects affected / exposed	3 / 101 (2.97%)	8 / 103 (7.77%)	
occurrences (all)	3	11	
Haemorrhoids			
subjects affected / exposed	0 / 101 (0.00%)	7 / 103 (6.80%)	
occurrences (all)	0	7	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	15 / 101 (14.85%)	7 / 103 (6.80%)	
occurrences (all)	16	7	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 101 (5.94%)	1 / 103 (0.97%)	
occurrences (all)	7	2	
Cough			
subjects affected / exposed	5 / 101 (4.95%)	3 / 103 (2.91%)	
occurrences (all)	5	8	
Oropharyngeal pain			
subjects affected / exposed	5 / 101 (4.95%)	3 / 103 (2.91%)	
occurrences (all)	5	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 101 (6.93%)	3 / 103 (2.91%)	
occurrences (all)	8	3	
Alopecia			
subjects affected / exposed	5 / 101 (4.95%)	4 / 103 (3.88%)	
occurrences (all)	5	4	
Pruritus			

subjects affected / exposed	5 / 101 (4.95%)	5 / 103 (4.85%)	
occurrences (all)	5	17	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 101 (10.89%)	11 / 103 (10.68%)	
occurrences (all)	12	11	
Arthralgia			
subjects affected / exposed	10 / 101 (9.90%)	10 / 103 (9.71%)	
occurrences (all)	15	11	
Musculoskeletal pain			
subjects affected / exposed	7 / 101 (6.93%)	3 / 103 (2.91%)	
occurrences (all)	8	6	
Muscle spasms			
subjects affected / exposed	5 / 101 (4.95%)	4 / 103 (3.88%)	
occurrences (all)	5	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 101 (8.91%)	17 / 103 (16.50%)	
occurrences (all)	10	23	
Urinary tract infection			
subjects affected / exposed	8 / 101 (7.92%)	11 / 103 (10.68%)	
occurrences (all)	13	13	
Upper respiratory tract infection			
subjects affected / exposed	3 / 101 (2.97%)	6 / 103 (5.83%)	
occurrences (all)	5	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 101 (9.90%)	9 / 103 (8.74%)	
occurrences (all)	11	11	
Diabetes mellitus			
subjects affected / exposed	9 / 101 (8.91%)	4 / 103 (3.88%)	
occurrences (all)	9	5	
Dehydration			
subjects affected / exposed	5 / 101 (4.95%)	1 / 103 (0.97%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2007	Protocol Amendment 1 • Inclusion criteria modification addition of subject with gastrinomas and tumours of unknown origin; extension of the window for the tumour biopsy. • Clarification on safety assessment (removal of local tolerance and disease progression from adverse event, role of the DSMC). • Clarification on procedures (blood sampling conditions and study drug injection). • Clarification on statistical definitions and testing. • Removal of plans for an interim analysis on the study and addition of a SSR.
30 July 2007	Protocol Amendment 2 • Modification of the inclusion criteria (tumour biopsy and CT-scan window • Specification about the randomisation list to be provided to the independent statistician in charge of reporting for DSMC.
30 April 2008	Protocol Amendment 3 • Introduction of the plan for an extension study to enable subjects to continue to receive lanreotide Autogel after completion of 96 weeks of treatment and to allow any subject that progressed while on placebo, to enter into the extension study. A request would be made by the Investigator for a potential code break due to centrally assessed disease progression confirmed by RECIST to verify subject's entry into the extension study.
04 April 2009	Protocol Amendment 4 • Change of saline solution in the United States of America. • Change of Sponsor name and address and of coordinating office name.
05 March 2010	Protocol Amendment 5 • Addition of hepatic tumour load evaluation on subject CT/MRI scan at baseline visit. • Removal of restriction regarding centres recruiting more than 20 subjects. • Addition of sensitivity analyses to investigate the robustness of the results of the primary efficacy analysis.
11 February 2011	Protocol Amendment 6 • Changes in response to US FDA to use the log rank test instead of the Cox PH model originally planned for the primary analysis of PFS, to follow up subjects for OS and to analyse OS as a secondary endpoint. • Planned update to CRF and ICF to collect OS data. • Change to the number of SSRs to one in response to advice from the FDA that this should be sufficient.
28 February 2012	Protocol Amendment 7 •To replace Ipsen Pharma S.A. with new laboratories, performing the PK evaluation and anti lanreotide antibody testing, due to site closure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported